

DISCUSSION OF THE AMENDMENT

Due to the length of the specification herein, Applicants will cite to the paragraph number of the published patent application (PG Pub) of the present application, i.e., US 2007/0149607, when discussing the application description, both in this section and in the Remarks section, *infra*, rather than to page and line of the specification as filed.

Claim 1 has been amended by deleting the superfluous term “characterized by”. Each of Claims 4 and 5 has been amended to depend on Claim 1 or 2 only.

No new matter is believed to have been added by the above amendment. Claims 1-24 remain pending in the application. Claims 1-5 are active; Claims 6-24 stand withdrawn from consideration.

REMARKS

Applicants thank the Examiner for the courtesy extended to Applicants' attorney during the interview held May 14, 2009, in the above-identified application. During the interview, Applicants' attorney explained the presently-claimed invention and why it is patentable over the applied prior art, and discussed other issues raised in the Office Action. The discussion is summarized and expanded upon below.

The rejection of Claims 1-5 under 35 U.S.C. § 103(a) as unpatentable over US 5,707,987 (Nakagawa et al) in view of EP 0449191 A1 (EP '191) and March's Advanced Organic Chemistry, 5th ed., 2001 (March), is respectfully traversed.

The invention of the presently-active claims is drawn to a method of preparing a compound having a formula (f), which is used as an intermediate to make a compound known to exhibit an excellent VLA-4 inhibitory effect, and having a formula (1) as described in the specification at paragraph [0004]. The method of the presently-active claims, as described in the specification at paragraph [0013], begins with a compound having formula (a), i.e., cis-4-hydroxy-L-proline as the starting material. Thus, the present invention provides a method that is capable of producing a compound (f) by using a cis-form compound (a) as a starting material. This method has a number of technological advantages, such as the number of intermediate steps can be reduced considerably and no Mitsunobu reaction occurs.

Nakagawa et al and EP '191 are both drawn to particular carbapenem derivatives, which are a different class of compounds from the above-discussed compounds of formula (1).

The Examiner relies on the first three steps of Reference Example 1 of EP '191, as the first three steps in ultimately preparing (2S,4S)-4-mercaptop-N-(p-nitrobenzyloxycarbonyl)-2-(2-pyrrolidon-4-yl)pyrrolidine (pages 109-110). In step 1, trans-L-hydroxyproline methyl ester hydrochloride is reacted with 2-(t-butoxycarbonylthio)-4,6-dimethylpyrimidine to

obtain N-t-butoxycarbonyl-L-hydroxyproline methyl ester, which in step 2 is reacted with t-butyldimethyldisilyl chloride to obtain (2S,4R)-N-t-butoxycarbonyl-4-t-butyldimethylsiloxy-L-proline methyl ester, which in step 3 is reduced to obtain (2S,4R)-N-t-butoxycarbonyl-4-t-dimethylsiloxy-2-hydroxymethylpyrrolidine (compound A).

The Examiner relies on Reference Example 100 of Nakagawa et al (column 133, line 45ff), particularly Steps 1 and 2 thereof, in which mesylchloride is reacted with the compound of Reference Example 1-3 of EP '191, i.e., compound A, to obtain (2S,4R)-N-t-butoxycarbonyl-4-t-butyldimethylsiloxy-2-(mesyloxymethyl)pyrrolidine, which compound is then reacted with methyl p-hydroxybenzoate to give (2S,4R)-N-t-butoxycarbonyl-4-t-butyldimethylsiloxy-2-[4-methoxycarbonyl]phenoxyethyl]pyrrolidine.

The Examiner relies on March, which the Examiner finds “teaches related methods of modifying and protecting the desired groups in a larger synthetic scheme. In addition, the reference teaches the use of various leaving groups such as aryl sulfonyl halides (tosyl).” However, while the Examiner cites the entire chapter 10 of March, which contains almost 200 pages of substantive text, the Examiner has not cited to particular portions thereof, in contravention of the requirement in 37 C.F.R. § 1.104(c)(2) that “the particular part relied on must be designated as nearly as practicable.”

Nevertheless, the above-applied combination of prior art does not disclose or suggest the specific method of the present claims. As Applicants’ attorney pointed out during the above-referenced interview, the Examiner has not explained why it would have been obvious to make the specific compound of formula (f) beginning with the compound of formula (a) as the starting material, let alone the intermediate steps to get there. EP '191 begins with **trans**-L-hydroxyproline methyl ester hydrochloride, not the **cis**-4-hydroxy-L-proline of the present claims. Where is the suggestion to use an acid in place of an ester thereof, and the **cis**-isomer

in place of the trans-isomer of EP '191? There is none. Nor is such a compound reacted with an alkyl halide in EP '191.

Thus, Nakagawa et al discloses a method in which a trans-form compound is used as a starting material (columns 133 and 134). In order to obtain its target compound (wherein the pyrrolidine ring has a cis-form substituent and also has a lower alkoxy group at position 4), this method requires a great number of intermediate steps, in contrast with the present invention. Furthermore, this method is not capable of blocking the occurrence of a Mitsunobu reaction. Specifically, as can be seen from step 9 of the scheme (columns 133-134), Nakagawa et al demonstrates the conversion of a trans-form of pyrrolidine ring containing MsO into a cis-form of the otherwise same compound but containing AcS.

However, it should be noted that this conversion is not possible unless the substituent is AcS. In other words, such conversion does not work well, when the substituent is a lower alkoxy group, OH or the like. If, under this scheme, one skilled in the art would want to make the position 4 of the pyrrolidine ring substituted with a lower alkoxy group in a cis-form, it would be necessary to rely upon a quite different method in which the conformation of OH is reversed by a Mitsunobu reaction at Step 8 and then is replaced by a lower alkoxy group. Thus, it is evident that the method of Nakagawa et al requires multiple steps and cannot help but resort to a Mitsunobu reaction to obtain the same conformation, in contrast to the presently-claimed invention. See also the discussion of such problems at paragraph [0006] of the specification herein.

The Examiner appears to view 'Me' in the "OMe" group at position 4 of the pyrrolidine ring as a protection group. It is not, because the Me moiety is merely one of the components embraced by the entire structure, not a protection group. The claimed method of the present invention requires no protection group at position 4 of the pyrrolidine ring and therefore is superior to that of Nakagawa et al in terms of simplicity.

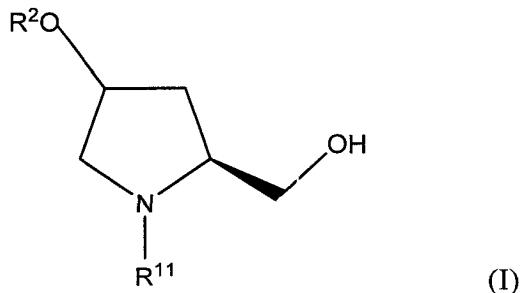
The Examiner's conclusion is clearly based on hindsight, and would not be made by a person of ordinary skill in the art without the present disclosure as a guide. In other words, the motivation to carry out the particular process steps recited herein comes only from Applicants' disclosure. Thus, and as noted by Applicants' attorney during the interview, what Applicants have done is used as a guide by the Examiner in order to find perceived analogues in the prior art. However, there is no disclosure or suggestion in the applied prior art to do what Applicants have done. Compare *In re Ochiai*, 71 F.3d 1565, 37 USPQ2d 1127 (Fed. Cir. 1995) (There is no per se rule that process claim is obvious if prior art references disclose same general process using "similar" starting materials; application of such rule is improper, since it sidesteps particularized obviousness inquiry required by 35 USC 103 and necessarily produces erroneous results.) and *In re Brouwer*, 77 F.3d 422, 37 USPQ2d 1663, 1666 (Fed. Cir. 1996) ("Without first knowing Brouwer's claimed process steps or the composition resulting from those steps, there is simply no suggestion in the references cited by the examiner to practice the claimed process. It is therefore not *prima facie* obvious.")
(copies of *Ochiai* and *Brouwer* enclosed).

For all the above reasons, it is respectfully requested that this rejection be withdrawn.

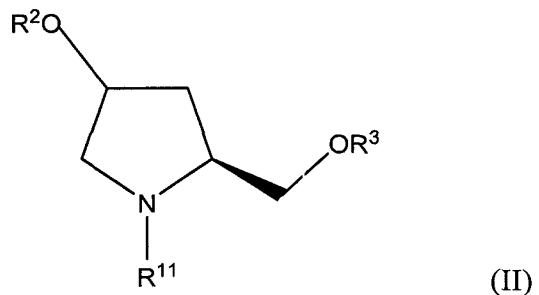
The rejection of Claims 1-5 on the ground of nonstatutory obviousness-type double patenting over Claims 1-5 of US 7,345,179 (Nakayama et al), is respectfully traversed. The Examiner finds that the starting material of the claims of Nakayama et al is compound (c) of the present claims "and the subsequent transformations substantially overlap in scope."

In reply, Claim 1 of Nakayama et al reads as follows:

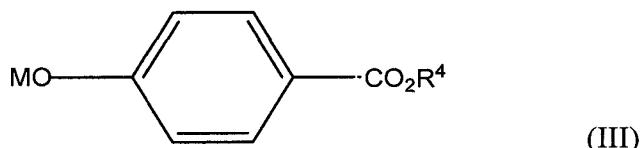
1. A process for producing a compound represented by formula (IV) as described below comprising reacting a compound represented by formula (I):



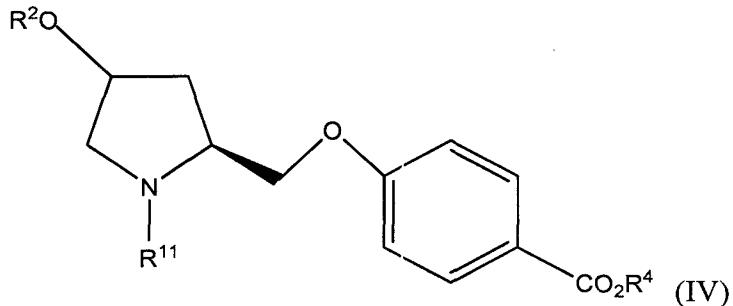
wherein R^{11} represents a protective group of amino group, and R^2 represents hydrogen atom or a protective group of hydroxy group (with the proviso that when both R^{11} and R^2 are protective groups, they are not the same protective group) with an optionally substituted arylsulfonyl chloride or an optionally substituted alkylsulfonyl chloride in the presence of a base to produce a compound represented by formula (II):



wherein R^{11} and R^2 are as defined above, and R^3 represents an optionally substituted arylsulfonyl group or an optionally substituted alkylsulfonyl group; reacting this compound with the compound represented by formula (III):



wherein R^4 is an optionally substituted alkyl group or an optionally substituted aralkyl group, and M represents an alkaline metal atom to obtain the compound represented by formula (IV):



wherein R¹¹, R², and R⁴ are as defined above.

Thus, and as Applicants' attorney explained during the interview, the starting compound of Nakayama et al is **not** the same as presently-recited compound (c). There is no suggestion in the claims of Nakayama et al to use the *cis*-form of their starting compound. Nor do the claims of Nakayama et al contain a disclosure or suggestion about earlier steps carried out to obtain presently-recited compound (c).

For all the above reasons, it is respectfully requested that this rejection be withdrawn.

The objection to Claims 4 and 5 is now moot in view of the above-discussed amendment. Accordingly, it is respectfully requested that the objection be withdrawn.

All of the presently-active claims in this application are now believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Respectfully submitted,

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